

Sodium Channel Blocker Compositions and the Use Thereof

The present application is a divisional of application Ser. No. 09/971,007, filed October 5, 2001, which is a continuation of International Application PCT/US00/09387, published under PCT Article 21(2) in English as WO 00/61188 on October 19, 2000, having an International filing date of April 10, 2000, and which claims the benefit under 35 U.S.C. § 119(e) to U.S. Provisional Application No. 60/128,543, filed April 9, 1999. The full disclosure of each of these applications is herein incorporated by reference.

Background of the Invention

Field of the Invention

This invention is in the field of medicinal chemistry. In particular, the invention relates to compositions comprising blockers of sodium (Na^+) channels and at least one of gabapentin or pregabalin. The invention also relates to methods for the treatment of chronic pain or convulsions comprising coadministering a sodium channel blocker and at least one of gabapentin or pregabalin.

Related Background Art

Several classes of therapeutically useful drugs, including local anesthetics such as lidocaine and bupivacaine, antiarrhythmics such as propafenone and amiodarone, and anticonvulsants such as lamotrigine, phenytoin and carbamazepine, have been shown to share a common mechanism of action by blocking or modulating Na^+ channel activity (Catterall, W.A., *Trends Pharmacol. Sci.* 8:57-65 (1987)). Each of these agents is believed to act by interfering with the rapid influx of Na^+ ions. Recently, other Na^+ channel blockers such as BW619C89 and lifarizine have been shown to be neuroprotective in animal models of global and focal ischemia and are presently in clinical trials (Graham *et al.*, *J. Pharmacol. Exp.*

Ther. 269:854-859 (1994); Brown *et al.*, *British J. Pharmacol.* 115:1425-1432 (1995); *SCRIP* 1870:8 (1993); *SCRIP* 1773:14 (1992)).

5 The neuroprotective activity of Na⁺ channel blockers is due to their effectiveness in decreasing extracellular glutamate concentration during ischemia by inhibiting the release of this excitotoxic amino acid neurotransmitter. Studies have shown that unlike glutamate receptor antagonists, Na⁺ channel blockers prevent hypoxic damage to mammalian white matter (Stys *et al.*, *J. Neurosci.* 12:430-439 (1992)). Thus, they may offer advantages for treating certain types of strokes or neuronal trauma where
10 damage to white matter tracts is prominent.

Another example of clinical use of a Na⁺ channel blocker is riluzole. This drug has been shown to prolong survival in a subset of patients with ALS (Bensimm *et al.*, *New Engl. J. Med.* 330:585-591 (1994)) and has subsequently been approved by the FDA for the treatment of ALS. In addition
15 to the above-mentioned clinical uses, carbamazepine, lidocaine and phenytoin are occasionally used to treat neuropathic pain, such as from trigeminal neurologia, diabetic neuropathy and other forms of nerve damage (Taylor and Meldrum, *Trends Pharmacol. Sci.* 16:309-316 (1995)), and carbamazepine and lamotrigine have been used for the treatment of manic depression
20 (Denicott *et al.*, *J. Clin. Psychiatry* 55: 70-76 (1994)).

It has been established that there are at least five to six sites on the voltage-sensitive Na⁺ channels which bind neurotoxins specifically (Catterall, W.A., *Science* 242:50-61 (1988)). Studies have further revealed that therapeutic antiarrhythmics, anticonvulsants and local anesthetics whose
25 actions are mediated by Na⁺ channels, exert their action by interacting with the intracellular side of the Na⁺ channel and allosterically inhibiting interaction with neurotoxin receptor site 2 (Catterall, W.A., *Ann. Rev. Pharmacol. Toxicol.* 10:15-43 (1980)).

Chronic pain or neuropathic pain is a heterogenous disease state with
30 an unclear etiology. In chronic pain, the pain can be mediated by multiple mechanisms. This type of pain generally arises from injury to the peripheral or central nervous tissue. The syndromes include pain associated with spinal

cord injury, multiple sclerosis, post-herpetic neuralgia, trigeminal neuralgia, phantom pain, causalgia and reflex sympathetic dystrophy and lower back pain. The chronic pain is different from acute pain in that patients suffer the abnormal pain sensations that can be described as spontaneous pain, continuous superficial burning and/or a deep aching pain. The pain can be evoked by heat-, cold- and mechano-hyperalgesia or by heat-, cold- and mechano-allodynia (International association for the study of pain: The classification of chronic pain (1995); Bennett G.J. Molecular Neurobiology of Pain, Progress in Pain Research and Management Vol. 9, pp. 109-113, edited by D. Borsook, 1997). In most cases, chronic neuropathic pain responds poorly to treatment with opiates or nonsteroidal anti-inflammatory analgesia.

Carbamazepine (TegretolTM), a sodium channel blocker anticonvulsant, has been shown to be effective in trigeminal neuralgia. However, one third of patients cannot tolerate the drug in the dose required to alleviate the pain (Victor *et al.*, Harrison's Principles of Internal Medicine. 11th ed. New York: McGraw-Hill 1987; 2035-40). In addition, carbamazepine may cause aplastic anemia, agranulocytosis, and hypersensitivity reaction (Canavero *et al.*, *Pain* 60:229-31 (1995)). These serious side effects are dose related. Carbamazepine is the only drug approved by the FDA for this indication.

There are no other drugs thus far that have been approved for chronic pain. Lamotrigine (Lamictal) is a sodium channel blocker that has been approved by the FDA for treating convulsions. This drug has also been shown to be effective for treating chronic pain (Lundardi *et al.*, *Neurology* 48: 1714 (1997)). However, the doses required for the treatment of chronic pain are relatively high and result in side effects. The major side effect of this drug is severe, potentially life-threatening rashes (Dichter and Brodie, *New Engl. J. Med.* 334: 1583 (1996)).

Gabapentin (NeurontinTM), an anticonvulsant with unknown mechanism of action has been shown recently to be efficacious for treating chronic pain (Rowbotham *et al.*, *JAMA* 280: 1837-1842 (1998) and Backonja *et al.*, *JAMA* 280: 1831-1836 (1998)). However, higher doses are necessary to treat chronic pain. Side effects such as exacerbated absence seizures and

nausea are associated with these high doses in addition to being fetotoxic. In addition, in clinical trials, gabapentin showed limited efficacy (i.e., less than 50% of patient population showed effectiveness, whereas 15-20% of patients treated with placebo showed effectiveness).

5 Pregabalin is a potent follow-up compound to gabapentin. The compound has similar activity to gabapentin and is currently under clinical trials for neuropathic pain (*SCRIP 2330:8* (1998)).

10 Thus, a need exists for treatments of chronic pain and convulsions that avoid the side effects exhibited by lamotrigine, carbamazepine and gabapentin. The present invention provides compositions and methods which reduces such side effects and improves the response rate of patients.

Summary of the Invention

15 The present invention relates to pharmaceutical compositions, comprising a first agent which is a sodium channel blocker, and a second agent selected from the group consisting of gabapentin, pregabalin, salts thereof and combinations thereof; wherein the total amount of said first agent and said second agent is effective to treat, prevent or ameliorate chronic pain or convulsions. Preferably, said first agent and said second agent are present in synergistic amounts, that is the sodium channel blocker and at least one of gabapentin or pregabalin or their salts are present in amounts lower than those used to treat or prevent chronic pain or convulsions when used alone. The invention further relates to such compositions that further comprise a pharmaceutically acceptable carrier, and optionally include pharmaceutically acceptable excipients.

25 The invention also relates to a method of treating, preventing or ameliorating chronic pain or convulsions, comprising administering to a patient in need thereof a first agent which is a sodium channel blocker, and a second agent selected from the group consisting of gabapentin, pregabalin, salts thereof and combinations thereof; wherein the total amount of said first agent and said second agent is effective to treat, prevent or ameliorate chronic

30

pain or convulsions. Preferably, said sodium channel blocker and at least one of gabapentin and pregabalin are administered in synergistic amounts. Preferably, the two agents are administered substantially simultaneously as defined herein. The sodium channel blocker and at least one of gabapentin and pregabalin may be administered separately or as part of a single pharmaceutical composition.

The invention also relates to a kit for the treatment of chronic pain or convulsions comprising a carrier containing one or more containers one of which comprises a sodium channel blocker and another of which comprises an agent selected from the group consisting of gabapentin, pregabalin, salts thereof and combinations thereof.

Description of the Figure

FIG. 1 depicts a graph showing the synergistic antiallodynic effect of gabapentin and the sodium channel blocker 4-(4'-fluorophenoxy)benzaldehyde semicarbazone (Co 102862) in the Chung model of neuropathic pain in rats (Kim and Chung, *Pain* 50: 355-363 (1992)).

Detailed Description of the Invention

The present invention arises out of the discovery that administration of a sodium channel blocker with gabapentin, pregabalin, salts thereof or combinations thereof, is effective for the treatment, prevention and/or amelioration of chronic pain and convulsions. The present invention also arises out of the discovery that it is possible to treat, prevent and/or ameliorate chronic pain and convulsions with synergistic amounts of at least one sodium channel blocker together with gabapentin, pregabalin or salts thereof or combinations thereof.

Useful first agents and second agents are described in the sections below. The first agent can be a single sodium channel blocker, or can two or

more sodium channel blockers. Likewise, the second agent can be a single compound or can be a mixture of two or more compounds.

5 The present invention relates to pharmaceutical compositions, comprising a first agent which is a sodium channel blocker, and a second agent selected from the group consisting of gabapentin, pregabalin, salts thereof and combinations thereof; wherein the total amount of said first agent and said second agent is effective to treat, prevent or ameliorate chronic pain or convulsions. Preferably, said first agent and said second agent act in synergy to treat, prevent or ameliorate chronic pain or convulsions. The
10 invention further relates to such compositions that further comprise a pharmaceutically acceptable carrier, and optionally include pharmaceutically acceptable excipients.

The invention also relates to a method of treating, preventing or ameliorating chronic pain or convulsions, comprising administering to a
15 patient in need thereof a first agent which is a sodium channel blocker, and a second agent selected from the group consisting of gabapentin, pregabalin, salts thereof and combinations thereof; wherein the total amount of said first agent and said second agent is effective to treat, prevent or ameliorate chronic pain or convulsions. Preferably, said sodium channel blocker and at least one
20 of gabapentin and pregabalin are administered in synergistic amounts. Preferably the agents are administered substantially simultaneously. The sodium channel blocker and at least one of gabapentin and pregabalin may be administered separately or as part of a single pharmaceutical composition in the treatment of pain, especially for treatment of chronic pain disorders. Such
25 disorders include, but are not limited to, inflammatory pain, postoperative pain, osteoarthritis pain associated with metastatic cancer, trigeminal neuralgia, acute herpetic and postherpetic neuralgia, diabetic neuropathy, causalgia, brachial plexus avulsion, occipital neuralgia, reflex sympathetic dystrophy, fibromyalgia, gout, phantom limb pain, burn pain, and other forms
30 of neuralgic, neuropathic, and idiopathic pain syndromes.

Thus, one aspect of the present invention is a method for the treatment of pain as listed above. Pain such as inflammatory pain, neuropathic pain,

cancer pain, postoperative pain, and idiopathic pain which is pain of unknown origin, for example, phantom limb pain are included especially. Neuropathic pain is caused by injury or infection of peripheral sensory nerves. It includes, but is not limited to pain from peripheral nerve trauma, herpes virus infection, diabetes mellitus, causalgia, plexus avulsion, neuroma, limb amputation, and vasculitis. Neuropathic pain is also caused by nerve damage from chronic alcoholism, human immunodeficiency virus infection, hypothyroidism, uremia, or vitamin deficiencies. Neuropathic pain includes, but is not limited to pain caused by nerve injury such as, for example, the pain from which diabetics suffer.

Another aspect of the invention is directed to a method for treating convulsions as described above.

Gabapentin and Pregabalin

One agent employed in the composition and methods of the present invention (referred to as the second agent) is a derivative of GABA (4-aminobutanoic acid). Gabapentin is a generic term used to identify the compound 1-(aminomethyl)cyclohexanecarboxylic acid. The compound can also exist as a hydrate, and the compound can exist in an amorphous or crystalline form. For example, U.S. Patent No. 4,894,476 discloses crystalline gabapentin monohydrate and a method for making it. PCT Published Application No. WO99/61408 discloses a non-hydrated gabapentin polymorph. PCT Published Application No. 98/28255 discloses alternate crystal forms of gabapentin (form II and form III) and methods for making these forms. Gabapentin is useful in the present invention in all of its forms. Preferred forms include those forms described in U.S. Patent Nos. 4,024,175, 4,087,544 and 4,894,476. Gabapentin can also form salts, for example a hydrochloride salt. Salts of gabapentin are included within the scope of the invention.

Pregabalin is a generic term used to identify the compound 3-(aminomethyl)-5-methylhexanoic acid. This compound has a stereocenter and

the 3S-enantiomer, (3S)-3-(aminomethyl)-5-methylhexanoic acid is the more active stereoisomer. Racemic mixtures or mixtures having an enantiomeric excess of the 3S stereoisomer are preferred for the present invention. The compound is useful in the present invention in all of its forms, whether
5 amorphous or crystalline, anhydrous or hydrated. Pregabalin can also exist in salt forms, which are included within the scope of the invention.

Gabapentin and pregabalin can be formulated to provide greater stability to the compound. Useful excipients for inclusion with gabapentin and pregabalin include neutral amino acids, such as glycine and L-valine; and
10 humectants, such as ethylene glycol, propylene glycol and glycerine. The active compounds may also be coated as agglomerated powders with a polymer such as polyvinyl pyrrolidone to provide better stability and processing characteristics.

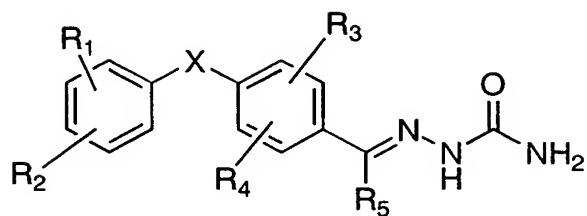
15 *Sodium Channel Blockers*

The first agent in the compositions and methods of the present invention is a sodium channel blocker.

Compounds can be tested for their Na⁺ channel blocking activity by the
20 electrophysiological and binding assays which are described herein. Preferred sodium channel blocking properties exhibit an K_i of about 100 μM or less in the electrophysiological assay. Preferably, the sodium channel blockers exhibit an K_i of 10 μM or less. Most preferably, the sodium channel blockers exhibit an K_i of about 1.0 μM or less.

25 Sodium channel blockers that may be used in the practice of the invention include any of the known sodium channel blockers as described herein, including compounds disclosed in the following documents.

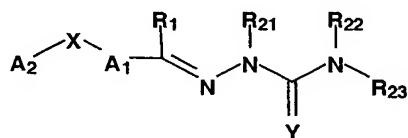
PCT International Published Application WO96/40628 discloses semicarbazones represented by Formula I:



I

where R₁-R₄ are independently hydrogen, halogen, C₁₋₉ alkyl, C₃₋₉ cycloalkyl, cyano, C₁₋₉ alkoxy, or C₆₋₁₀ aryloxy; R₅ is hydrogen, C₁₋₉ alkyl, C₃₋₉ cycloalkyl, or C₆₋₁₀ aryl; and X is oxygen or sulfur. The compounds are disclosed to be useful as anticonvulsants.

PCT International Published Application WO98/47869 discloses the compounds claimed in WO 96/40628 act as sodium channel blockers. In addition, it discloses sodium channel blocking semicarbazones and thiosemicarbazones represented by Formula II:



II

or a pharmaceutically acceptable salt or prodrug thereof, wherein:

Y is oxygen or sulfur;

R₁ is hydrogen, alkyl, cycloalkyl, alkenyl, alkynyl, haloalkyl, aryl, aminoalkyl, hydroxyalkyl, alkoxyalkyl or carboxyalkyl;

R₂₁, R₂₂ and R₂₃ are independently hydrogen, alkyl, cycloalkyl, alkenyl, alkynyl, haloalkyl, aryl, aminoalkyl, hydroxyalkyl, alkoxyalkyl or carboxyalkyl, or R₂₁, is defined as above, and R₂₂ and R₂₃ together with the nitrogen atom to which they are attached form a heterocycle, including piperidine, piperazine, or morpholine;

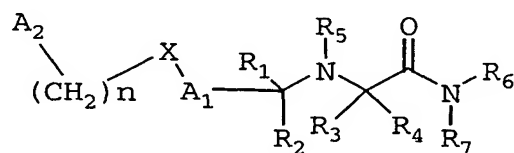
A₁ and A₂ are independently aryl, heteroaryl, saturated or partially unsaturated carbocycle or saturated or partially unsaturated heterocycle, any of which is optionally substituted;

X is one or O, S, NR₂₄, CR₂₅R₂₆, C(O), NR₂₄C(O), C(O)NR₂₄, SO, SO₂ or a covalent bond; where

R₂₄ is hydrogen, alkyl, cycloalkyl, alkenyl, alkynyl, haloalkyl, aryl, aminoalkyl, hydroxyalkyl, alkoxyalkyl or carboxyalkyl; and

R₂₅ and R₂₆ are independently hydrogen, alkyl, cycloalkyl, alkenyl, alkynyl, haloalkyl, aryl, aminoalkyl, hydroxyalkyl, alkoxyalkyl or carboxyalkyl.

**PCT International Published Application WO99/26614 (Appl. No. PCT/US98/24965, filed November 20, 1998), discloses sodium channel blockers represented by Formula III:



III

or a pharmaceutically acceptable salt or prodrug thereof, wherein:

R₁, R₂, R₃ and R₄ are independently hydrogen, alkyl, cycloalkyl, alkenyl, alkynyl, haloalkyl, aryl, aminoalkyl, hydroxyalkyl, alkoxyalkyl or carboxyalkyl;

R₅, R₆ and R₇ are independently hydrogen, alkyl, cycloalkyl, alkenyl, alkynyl, haloalkyl, aryl, aminoalkyl, hydroxyalkyl, alkoxyalkyl or carboxyalkyl, or R₅ is defined as above, and R₆ and R₇ together with the nitrogen atom to which they are attached form a heterocycle;

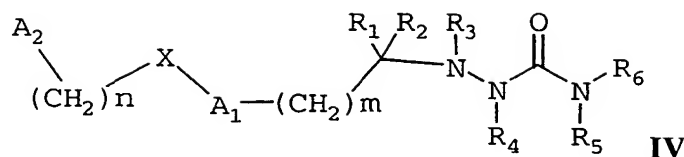
A₁ and A₂ are independently aryl, heteroaryl, saturated or partially unsaturated carbocycle or saturated or partially unsaturated heterocycle, any of which is optionally substituted;

X is one or O, S, NR₈, CH₂, C(O), NR₈C(O), C(O)NR₈, SO, SO₂ or a covalent bond; where

R₈ is hydrogen, alkyl, cycloalkyl, alkenyl, alkynyl, haloalkyl, aryl, aminoalkyl, hydroxyalkyl, alkoxyalkyl or carboxyalkyl;

n is 0, 1, 2 or 3.

** PCT International Published Application WO 99/39712 (Appl. No. PCT/US99/02419, filed February 4, 1999), discloses sodium channel blockers represented by Formula IV:



or a pharmaceutically acceptable salt or prodrug thereof, wherein:

5 R_1 and R_2 are independently hydrogen, alkyl, cycloalkyl, alkenyl, alkynyl, haloalkyl, aryl, aminoalkyl, hydroxyalkyl, alkoxyalkyl or carboxyalkyl;

R_3 , R_4 , R_5 and R_6 are independently hydrogen, alkyl, cycloalkyl, alkenyl, alkynyl, haloalkyl, aryl, aminoalkyl, hydroxyalkyl, alkoxyalkyl or carboxyalkyl, or R_3 and R_4 is defined as above, and R_5 and R_6 together with the nitrogen atom to which they are attached form a heterocycle, including
10 piperidine, piperazine, morpholine;

A_1 and A_2 are independently aryl, heteroaryl, saturated or partially unsaturated carbocycle or saturated or partially unsaturated heterocycle, any of which is optionally substituted;

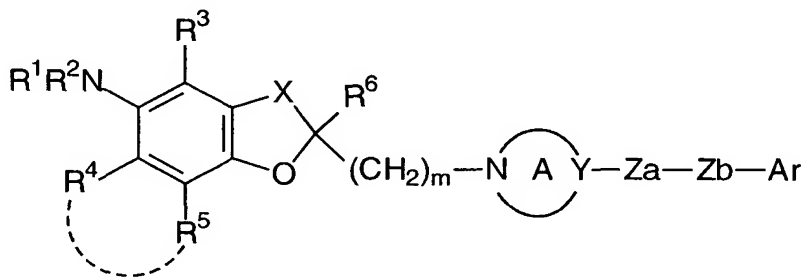
15 X is one of O, S, NR_7 , CH_2 , $C(O)$, $NR_7C(O)$, $C(O)NR_7$, SO, SO_2 or a covalent bond; where

R_7 is hydrogen, alkyl, cycloalkyl, alkenyl, alkynyl, haloalkyl, aryl, aminoalkyl, hydroxyalkyl, alkoxyalkyl or carboxyalkyl;

n is 0, 1, 2 or 3.

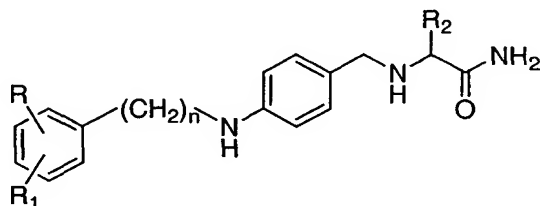
20 m is 0, 1, 2, or 3.

PCT International Published Application WO98/08842 discloses sodium channel blockers having the Formula V:



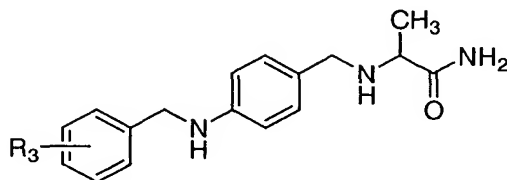
wherein R^1 and R^2 each represents hydrogen, lower alkyl which may be substituted or acyl; R^3 , R^4 and R^5 each represents lower alkyl which may be substituted or lower alkoxy which may be substituted or R^4 or R^5 taken together represent a 5- or 6-membered carbocyclic group; R^6 represents lower alkyl; Ar represents an aromatic group which may be substituted; ring A represents a 5- to 8-membered nitrogen-containing heterocyclic ring which may be substituted; X represents lower alkylene which may be substituted; Y represents carbon or nitrogen; Za represents CH_2 , $COCH_2$, OCH_2 , SCH_2 , $NHCH_2$, etc.; Zb represents a bond or a divalent aliphatic hydrocarbon group which may be substituted and may contain O, N or S; and m represents an integer of 1 to 3, or a salt thereof.

U.S. Patent No. 5,449,692 discloses compounds having Formula VI:



VI

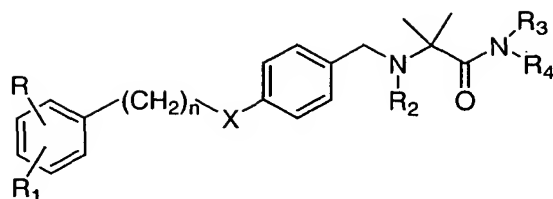
wherein n is an integer of 1 to 4; each of R and R_1 , which may be the same or different, is hydrogen, halogen, trifluoromethyl or C_1 - C_4 alkoxy; R_2 is hydrogen or C_1 - C_4 alkyl; and a pharmaceutically acceptable salts thereof; and wherein when, at the same time, R is hydrogen, R_1 is hydrogen or halogen and n is one, then R_2 is other than hydrogen or methyl; and of Formula VIa:



VIa

wherein R_3 is halogen, and a pharmaceutical acceptable salt thereof.

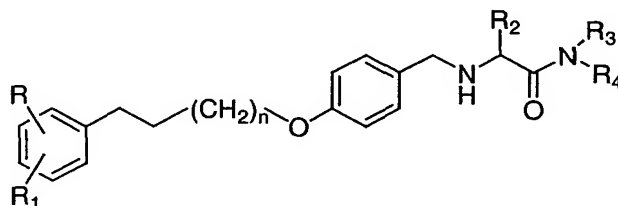
Other sodium channel blocker compounds useful in the practice of the invention include compounds disclosed in PCT International Published Application WO 97/05102 having Formula VII:



VII

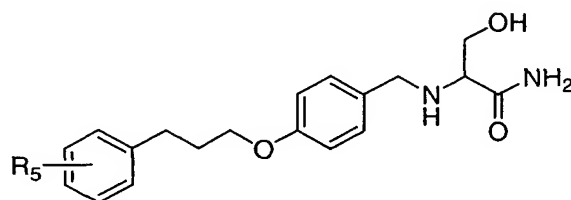
wherein n is zero, 1, 2 or 3; X is -O-, -S-, -CH₂- or -NH-; each of R and R₁ independently is hydrogen, C₁-C₆ alkyl, halogen, hydroxy, C₁-C₄ alkoxy or trifluoromethyl; each of R₂, R₃ and R₄ independently is hydrogen, C₁-C₆ alkyl or C₃-C₇ cycloalkyl; and the pharmaceutically acceptable salts thereof.

Other sodium channel blocker compounds useful in the practice of the invention, include compounds disclosed in U.S. Patent No. 5,446,066 having Formula VIII:



VIII

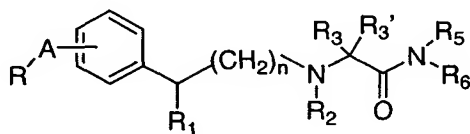
wherein n is zero or an integer of 1 to 3; each of R and R₁, which may be the same or different, is hydrogen, halogen, trifluoromethyl or C₁-C₄ alkoxy; R₂ is hydrogen or C₁-C₄ alkyl optionally substituted by hydroxy; each of R₃ and R₄ independently is hydrogen or C₁-C₄ alkyl; or a pharmaceutically acceptable salt thereof; and of Formula VIIIa:



VIIIa

wherein R₅ is hydrogen, halogen, trifluoromethyl or C₁-C₄ alkoxy, or a pharmaceutically acceptable salt thereof.

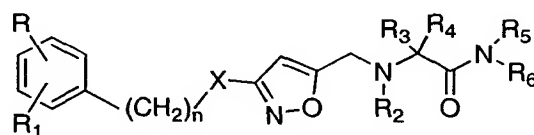
Other sodium channel blocker compounds useful in the practice of the invention include compounds disclosed in U.S. Patent No. 5,236,957 having Formula IX:



IX

5 wherein R is C₁-C₈ alkyl, C₃-C₈ cycloalkyl, furyl, thienyl, pyridyl or unsubstituted or substituted phenyl; A is a -(CH₂)_m- or -(CH₂)_p-X-(CH₂)_q- group wherein X is -O-, -S- or -NR₄-; R₁, R₂, R₃, and R₃' are hydrogen or C₁-C₆ alkyl, n, m, p, and q are zero or an integer from 1 to 3; and each of R₅ and R₆ is independently hydrogen or C₁-C₆ alkyl, and the pharmaceutical acceptable salts thereof.

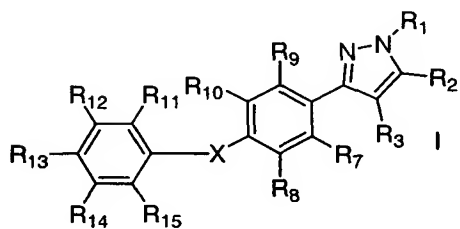
Other sodium channel blocker compounds useful in the practice of the invention include compounds disclosed in PCT International Published Application WO 98/43964 having Formula X:



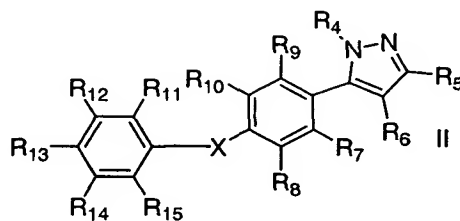
X

15 wherein n is zero, or an integer of 1 to 3; X is O, S or NH; each of R and R₁, which are the same or different, is hydrogen, C₁-C₆ alkyl, halogen, hydroxy, C₁-C₄ alkoxy or trifluoromethyl; each of R₂, R₅ and R₆, which are the same or different, is hydrogen or C₁-C₆ alkyl; each of R₃ and R₄, which are the same or different, is hydrogen or C₁-C₆ alkyl or R₃ or R₄ taken together with the adjacent carbon atom form a C₃-C₇ cycloalkyl ring; and their pharmaceutically acceptable salts.

Other sodium channel blocker compounds may be used in the practice of the invention, including compounds disclosed in U.S. Patent Application No. 60/126,553 having Formula **XI** and **XII**:



XI



XII

or a pharmaceutically acceptable salt, prodrug or solvate thereof, wherein:

10 R_1 and R_4 are independently selected from the group consisting of hydrogen, alkyl, cycloalkyl, aryl, aralkyl, $C(O)R_{16}$, $S(O)R_{16}$, SO_2R_{16} all of which may be optionally substituted;

15 R_2 , R_3 , R_5 and R_6 are independently selected from the group consisting of hydrogen, alkyl, cycloalkyl, alkenyl, alkynyl, haloalkyl, aryl, aminoalkyl, hydroxyalkyl, alkoxyalkyl, alkylthio, alkylsulfinyl, alkylsulfonyl or carboxyalkyl, or taken together with the carbon atoms to which they are attached to form a carbocycle or heterocycle. Examples of bridges formed by R_2 and R_3 or R_5 and R_6 taken together are $-OCH_2O-$, $-OCF_2O-$, $-(CH_2)_3-$, $-(CH_2)_4-$, $-OCH_2CH_2O-$, $-CH_2N(R_{17})CH_2-$, $-CH_2CH_2N(R_{17})CH_2-$, $-CH_2N(R_{17})CH_2CH_2-$ and $-CH=CH-CH=CH-$; where R_{17} is hydrogen, alkyl, cycloalkyl;

25 R_7 , R_8 , R_9 , R_{10} , R_{11} , R_{12} , R_{13} , R_{14} , and R_{15} are independently selected from the group consisting of hydrogen, halo, haloalkyl, aryl, cycloalkyl, saturated or partially unsaturated heterocycle, heteroaryl, alkyl, alkenyl, alkynyl, arylalkyl, arylalkenyl, arylalkynyl, heteroarylalkyl, heteroarylalkenyl, heteroarylalkynyl, cycloalkylalkyl, heterocycloalkyl, hydroxyalkyl, aminoalkyl, carboxyalkyl, alkoxyalkyl, nitro, amino, ureido, cyano, acylamido, hydroxy, thiol, acyloxy, azido, alkoxy, carboxy, carbonylamido or alkylthiol; or R_{11} and R_{12} or R_{12} and R_{13} are taken together with the carbon

atoms to which they are attached to form a carbocycle or heterocycle.

Examples of bridges formed by R₁₁ and R₁₂ or R₁₂ and R₁₃ taken together are

—OCH₂O—, —OCF₂O—, —(CH₂)₃—, —(CH₂)₄—, —OCH₂CH₂O—,
—CH₂N(R₁₇)CH₂—, —CH₂CH₂N(R₁₇)CH₂—, —CH₂N(R₁₇)CH₂CH₂— and
5 —CH=CH—CH=CH—; where R₁₇ is defined as above;

R₁₆ is selected from the group consisting of amino, alkyl, cycloalkyl,
aralkyl, aryl, or heteroaryl;

X is one of O, S, NR₁₇, CH₂, C(O), NR₁₇C(O), C(O)NR₁₇, SO, SO₂, or
a covalent bond where R₁₇ is defined as above.

10 Exemplary compounds that may be employed as blockers of sodium
channels in the compositions and methods of the present invention include,
without limitation:

Lidocaine;

Tetracaine;

15 Phenytoin;

Carbamazepine;

Lamotrigine;

5-(2,3,5-trichlorophenyl)-2,4-diamino-pyrimidine (BW1003C87);

4-amino-2-(4-methylpiperazine-1-yl)-5-(2,3,5-

20 trichlorophenyl)pyrimidine (BW619C89);

Zonisamide;

Riluzole;

Lifarizine;

(=)-*cis*-3,4-dichloro-*N*-methyl-*N*-[2-(1-pyrrolidinyl)-cyclohexyl]-

25 benzamide (U54494A);

N-[3-(2,6-dimethyl-1-piperidiny)]- α -phenylbenzeneacetamide
(PD85639);

Ralitoline;

N-(2-chloro-6-methylphenyl)-*N*-4-pyridinyl urea (CI953);

30 Fluarizine;

Verapamil;

Carvedilol;

- N*-acenaphth-5-yl-*N'*-4-methoxynaphthyl guanidine CNS1237;
Mexiletine;
Amitriptyline;
1-(4-(4-fluorophenoxy)benzyl)semicarbazide;
5 5-methylthio-3-(4-phenoxyphenyl)-1H-pyrazole-1-carboxamide;
5-methylsulfinyl-3-(4-phenoxyphenyl)-1H-pyrazole-1-carboxamide;
3-[4-(4-fluorophenoxy)phenyl]-1H-pyrazole-1-carboxamide;
3-[4-(4-nitrophenoxy)phenyl]-1H-pyrazole-1-carboxamide;
3-[4-(4-methoxyphenoxy)phenyl]-1H-pyrazole-1-carboxamide;
10 3-[4-(3-chloro-2-cyanophenoxy)phenyl]-1H-pyrazole-1-carboxamide;
3-[4-(2,4-difluorophenoxy)phenyl]-1H-pyrazole-1-carboxamide;
3-[4-(2-chloro-4-fluorophenoxy)phenyl]-1H-pyrazole-1-carboxamide;
1-[3-[4-(4-nitrophenoxy)phenyl]-1H-pyrazole]ethanone;
2-methyl-1-[3-(4-phenoxyphenyl)-1H-pyrazole]propanone;
15 3-[4-(4-fluorophenoxy)phenyl]-2H-pyrazole-2-carboxamide;
1-methanesulfonyl-3-(4-phenoxy)phenyl-1H-pyrazole;
1-(4-phenoxybenzyl)semicarbazide;
1-(4-(4-fluorophenoxy)benzyl)semicarbazide;
1-(4-(4-chlorophenoxy)benzyl)semicarbazide;
20 1-(4-(4-bromophenoxy)benzyl)semicarbazide;
1-(4-(4-methoxyphenoxy)benzyl)semicarbazide;
1-(4-(4-trifluoromethylphenoxy)benzyl)semicarbazide;
1-(4-(4-methylphenoxy)benzyl)semicarbazide;
1-(4-(3,4-difluorophenoxy)benzyl)semicarbazide;
25 1-(4-(4-chloro-2-fluorophenoxy)benzyl)semicarbazide;
1-(4-(4-nitrophenoxy)benzyl)semicarbazide;
1-(4-(3-methylphenoxy)benzyl)semicarbazide;
1-(4-(4-*t*-butylphenoxy)benzyl)semicarbazide;
1-(4-(4-propylphenoxy)benzyl)semicarbazide;
30 1-(4-(4-*s*-butylphenoxy)benzyl)semicarbazide;
1-(4-(3,4-methylenedioxyphenoxy)benzyl)semicarbazide;
1-(4-cyclohexyloxybenzyl)semicarbazide;

- 1-(4-cycloheptyloxybenzyl)semicarbazide;
1-(4-(5-indanyloxy)benzyl)semicarbazide;
1-(4-(6-quinolinyloxy)benzyl)semicarbazide;
1-(4-(4-fluorophenoxy)-3-fluorobenzyl)semicarbazide;
5 1-(4-(tetrahydropyraniloxy)benzyl)semicarbazide;
1-(4-(4-fluorophenoxy)benzyl)-4-methylsemicarbazide;
1-(4-(4-fluorophenoxy)benzyl)-2-methylsemicarbazide;
2-(4-(2-fluorobenzyloxy)benzylamino)-2-methyl-propanamide;
2-(4-(4-fluorophenoxy)benzylamino)-2-methyl-propanamide;
10 2-(4-(3,4-methylenedioxyphenoxy)benzylamino)-2-methyl-
propanamide;
2-(4-(3,4-methylenedioxybenzyloxy)benzylamino)-2-methyl-
propanamide;
2-(4-cyclohexyloxybenzylamino)-2-methyl-propanamide;
15 2-(4-(5,6,7,8-tetrahydro-2-naphthoxy)benzylamino)-2-methyl-
propanamide;
2-(4-(2-adamantanoxyl)benzylamino)-2-methyl-propanamide;
2-(4-(4-Chloro-2-fluorophenoxy)benzylamino)-2-methyl-propanamide;
2-(4-(2,4-difluorophenoxy)benzylamino)-2-methyl-propanamide;
20 2-(4-(3,4-difluorophenoxy)benzylamino)-2-methyl-propanamide;
2-(4-(6-bromo-4-fluorophenoxy)benzylamino)-2-methyl-propanamide;
2-(4-(4-nitrophenoxy)benzylamino)-2-methyl-propanamide;
2-(4-(4-tetrahydropyranoxy)benzylamino)-2-methyl-propanamide;
2-(4-(3,5-difluorophenoxy)benzylamino)-2-methyl-propanamide;
25 2-(4-(4-chlorophenoxy)benzylamino)-2-methyl-propanamide;
2-(4-(4-methylphenoxy)benzylamino)-2-methyl-propanamide;
2-(4-(2-chloro-4-fluorophenoxy)benzylamino)-2-methyl-propanamide;
2-(4-(5-indanoxyl)benzylamino)-2-methyl-propanamide;
2-(4-cycloheptoxybenzylamino)-2-methyl-propanamide;
30 2-(4-(1-methyl-4-piperidinoxy)benzylamino)-2-methyl-propanamide;
2-(4-(exo-2-norbornoxy)benzylamino)-2-methyl-propanamide;

2-(3-(4-fluorophenoxy)-5-pyridylmethylamino)-2-methyl-propanamide;

2-(4-(4-pyridinoxy)benzylamino)-2-methyl-propanamide;

2-(3-fluoro-4-(4-fluorophenyl)benzylamino)-2-methyl-propanamide;

5 2-(4-(2-pyrimidinoxy)benzylamino)-2-methyl-propanamide;

2-(4-(6-quinolinoxy)benzylamino)-2-methyl-propanamide;

2-(4-(N, N-diphenylamino)benzylamino)-2-methyl-propanamide;

2-(4-diphenylmethoxy)benzylamino-2-methyl-propanamide; and

2-(4-triphenylmethoxy)benzylamino-2-methyl-propanamide;

10 or pharmaceutically acceptable salts, hydrates or esters thereof.

Certain of the sodium channel blockers, gabapentin and pregabalin may exist as optical isomers and the invention includes both the racemic mixtures of such optical isomers as well as the individual enantiomers that may be separated according to methods that are well know to those of ordinary skill in the art.

The invention disclosed herein is meant to encompass all pharmaceutically acceptable salts thereof of the disclosed compounds. The pharmaceutically acceptable salts include, but are not limited to, metal salts such as sodium salt, potassium salt, cesium salt and the like; alkaline earth metals such as calcium salt, magnesium salt and the like; organic amine salts such as triethylamine salt, pyridine salt, picoline salt, ethanolamine salt, triethanolamine salt, dicyclohexylamine salt, N,N'-dibenzylethylenediamine salt and the like; inorganic acid salts such as hydrochloride, hydrobromide, sulfate, phosphate and the like; organic acid salts such as formate, acetate, trifluoroacetate, maleate, tartrate and the like; sulfonates such as methanesulfonate, benzenesulfonate, *p*-toluenesulfonate, and the like; amino acid salts such as arginate, asparaginate, glutamate and the like.

The invention disclosed herein is also meant to encompass prodrugs of the disclosed compounds. Prodrugs are considered to be any covalently bonded carriers which release the active parent drug *in vivo*. Examples of prodrugs include esters or amides of compounds having hydroxyalkyl or

aminoalkyl substituents, and these may be prepared by reacting such compounds with anhydrides such as succinic anhydride.

Some of the compounds disclosed herein may contain one or more asymmetric centers and may thus give rise to enantiomers, diastereomers, and other stereoisomeric forms. The present invention is also meant to encompass racemic mixtures, resolved forms mixtures thereof, as well as the individual enantiomers that may be separated according to methods that are well known to those of ordinary skill in the art. When the compounds described herein contain olefinic double bonds or other centers of geometric asymmetry, and unless specified otherwise, it is intended to include both E and Z geometric isomers. All tautomers are intended to be encompassed by the present invention as well.

As used herein, the term "stereoisomers" is a general term for all isomers of individual molecules that differ only in the orientation of their atoms in space. It includes enantiomers and isomers of compounds with more than one chiral center that are not mirror images of one another (diastereomers).

The term "chiral center" refers to a carbon atom to which four different groups are attached.

The term "enantiomer" or "enantiomeric" refers to a molecule that is nonsuperimposable on its mirror image and hence optically active wherein the enantiomer rotates the plane of polarized light in one direction and its mirror image rotates the plane of polarized light in the opposite direction.

The term "racemic" refers to a mixture of equal parts of enantiomers and which is optically inactive.

The term "resolution" refers to the separation or concentration or depletion of one of the two enantiomeric forms of a molecule. The phrase "enantiomeric excess" refers to a mixture wherein one enantiomer is present in a greater concentration than its mirror image molecule.

The sodium channel blockers, gabapentin and pregabalin may be prepared using methods known to those skilled in the art.

Compositions within the scope of this invention include all compositions wherein the sodium channel blockers, gabapentin and/or pregabalin are contained in an amount which is effective to achieve its intended purpose. The amount of sodium channel blockers, gabapentin and/or pregabalin is preferably less than the amount needed when each compound is used alone as a single agent. While individual needs vary, determination of optimal ranges of effective amounts of each component is within the skill of the art. Typically, the sodium channel blockers may be administered to mammals, e.g. humans, orally at a dose of 0.1 to 10 mg/kg, or an equivalent amount of the pharmaceutically acceptable salt thereof, per day of the body weight of the mammal being treated. Gabapentin and/or pregabalin may be administered orally at a dose of about 50 to about 3200 mg/day, preferably about 150 to about 2400 mg/day, and more preferably 300 to 1800 mg/day, or an equivalent amount of the pharmaceutically acceptable salt thereof. For intramuscular injection, the dose is generally about one-half of the oral dose. Typically, pregabalin can be administered at lower doses than gabapentin.

With respect to the first agent, exemplary unit oral doses comprise:
For carbamazepine, from about 50 to about 1500 mg/day, preferably about 100 to about 800 mg/day, more preferably about 100 to about 600 mg/day, and most preferably about 100 to about 400 mg/day; or
For lamotrigine, from about 50 to about 1200 mg/day, preferably 100 to about 600 mg/day, more preferably about 100 to about 450 mg/day, and most preferably about 100 to about 300 mg/day; or
For Co 102862, from about 50 to about 1200 mg/day, preferably from about 200 to about 900 mg/day, more preferably from about 200 to about 750 mg/day, and most preferably from about 200 to about 600 mg/day Co 102862.

Additional useful unit oral doses for the first agent include:
from about 400 to about 800 mg/day carbamazepine,
from about 200 to about 600 mg/day lamotrigine
from about 350 to about 900 mg/day Co 102862.

With respect to the second agent, exemplary unit oral doses comprise:

from about 100 to about 3200 mg/day gabapentin, preferably about 100 to about 1800 mg/day gabapentin, and more preferably from about 150 to about 900 mg/day gabapentin; or

from about 75 to about 900 mg/day pregabalin, preferably 75 to about 450 mg/day of pregabalin.

Another useful range is from about 300 to about 1800 mg/day of gabapentin. Another useful range is from about 150 to about 900 mg/day pregabalin.

The unit dose may be administered one or more times daily as one or more tablets.

In addition to administering the sodium channel blockers, gabapentin and pregabalin as a raw chemical, the compounds may be administered as part of a pharmaceutical preparation containing suitable pharmaceutically acceptable carriers comprising excipients and auxiliaries which facilitate processing of the compounds into preparations which can be used pharmaceutically. Preferably, the preparations, particularly those preparations which can be administered orally and which can be used for the preferred type of administration, such as tablets, dragees, and capsules, and also preparations which can be administered rectally, such as suppositories, as well as suitable solutions for administration by injection or orally, contain from about 0.01 to 99 percent, preferably from about 0.25 to 75 percent of active compound(s), together with the excipient.

Also included within the scope of the present invention are the non-toxic pharmaceutically acceptable salts of the sodium channel blockers, gabapentin and pregabalin. Acid addition salts are formed by mixing a solution of the particular compound with a solution of a pharmaceutically acceptable non-toxic acid such as hydrochloric acid, fumaric acid, maleic acid, succinic acid, acetic acid, citric acid, tartaric acid, carbonic acid, phosphoric acid, oxalic acid, dichloroacetic acid, and the like. Basic salts are formed by mixing a solution of the particular compound with a solution of a pharmaceutically acceptable non-toxic base such as sodium hydroxide, potassium hydroxide, choline hydroxide, sodium carbonate and the like.

The pharmaceutical compositions of the invention may be administered to any animal which may experience the beneficial effects of the compounds of the invention. Foremost among such animals are mammals, e.g., humans, although the invention is not intended to be so limited.

5 The pharmaceutical compositions of the present invention may be administered by any means that achieve their intended purpose. For example, administration may be by parenteral, subcutaneous, intravenous, intramuscular, intraperitoneal, transdermal, or buccal routes. Alternatively, or concurrently, administration may be by the oral route. The dosage
10 administered will be dependent upon the age, health, and weight of the recipient, kind of concurrent treatment, if any, frequency of treatment, and the nature of the effect desired.

 In the practice of the present invention, the sodium channel blockers, gabapentin and pregabalin are preferably administered substantially
15 simultaneously. By "substantially simultaneously" is intended to mean that the sodium channel blockers, gabapentin and/or pregabalin are administered in sequence or at the same time so long as effective blood levels of the sodium channel blockers, gabapentin and pregabalin are achieved at the same time. The first agent or the second agent can be administered first if sequential
20 administration is chosen. It is preferred that the sodium channel blockers, gabapentin and pregabalin are administered as part of a single dosage form.

 The pharmaceutical preparations of the present invention are manufactured in a manner which is itself known, for example, by means of conventional mixing, granulating, dragee-making, dissolving, or lyophilizing
25 processes. Thus, pharmaceutical preparations for oral use can be obtained by combining the active compounds with solid excipients, optionally grinding the resulting mixture and processing the mixture of granules, after adding suitable auxiliaries, if desired or necessary, to obtain tablets or dragee cores.

 Suitable excipients are, in particular, fillers such as saccharides, for
30 example lactose or sucrose, mannitol or sorbitol, cellulose preparations and/or calcium phosphates, for example tricalcium phosphate or calcium hydrogen phosphate, as well as binders such as starch paste, using, for example, maize

starch, wheat starch, rice starch, potato starch, gelatin, tragacanth, methyl cellulose, hydroxypropylmethylcellulose, sodium carboxymethylcellulose, and/or polyvinyl pyrrolidone. If desired, disintegrating agents may be added such as the above-mentioned starches and also carboxymethyl-starch, cross-linked polyvinyl pyrrolidone, agar, or alginic acid or a salt thereof, such as sodium alginate. Auxiliaries are, above all, flow-regulating agents and lubricants, for example, silica, talc, stearic acid or salts thereof, such as magnesium stearate or calcium stearate, and/or polyethylene glycol. Dragee cores are provided with suitable coatings which, if desired, are resistant to gastric juices. For this purpose, concentrated saccharide solutions may be used, which may optionally contain gum arabic, talc, polyvinyl pyrrolidone, polyethylene glycol and/or titanium dioxide, lacquer solutions and suitable organic solvents or solvent mixtures. In order to produce coatings resistant to gastric juices, solutions of suitable cellulose preparations such as acetyl-cellulose phthalate or hydroxypropylmethyl-cellulose phthalate, are used. Dye stuffs or pigments may be added to the tablets or dragee coatings, for example, for identification or in order to characterize combinations of active compound doses.

Other pharmaceutical preparations which can be used orally include push-fit capsules made of gelatin, as well as soft, sealed capsules made of gelatin and a plasticizer such as glycerol or sorbitol. The push-fit capsules can contain the active compounds in the form of granules which may be mixed with fillers such as lactose, binders such as starches, and/or lubricants such as talc or magnesium stearate and, optionally, stabilizers. In soft capsules, the active compounds are preferably dissolved or suspended in suitable liquids, such as fatty oils, or liquid paraffin. In addition, stabilizers may be added.

Possible pharmaceutical preparations which can be used rectally include, for example, suppositories, which consist of a combination of one or more of the active compounds with a suppository base. Suitable suppository bases are, for example, natural or synthetic triglycerides, or paraffin hydrocarbons. In addition, it is also possible to use gelatin rectal capsules which consist of a combination of the active compounds with a base. Possible

base materials include, for example, liquid triglycerides, polyethylene glycols, or paraffin hydrocarbons.

Suitable formulations for parenteral administration include aqueous solutions of the active compounds in water-soluble form, for example, water-soluble salts and alkaline solutions. In addition, suspensions of the active compounds as appropriate oily injection suspensions may be administered. Suitable lipophilic solvents or vehicles include fatty oils, for example, sesame oil, or synthetic fatty acid esters, for example, ethyl oleate or triglycerides or polyethylene glycol-400 (the compounds are soluble in PEG-400). Aqueous injection suspensions may contain substances which increase the viscosity of the suspension include, for example, sodium carboxymethyl cellulose, sorbitol, and/or dextran. Optionally, the suspension may also contain stabilizers.

Preferred sodium channel blocking properties exhibit an K_i of about 100 μM or less in the electrophysiological assay. Preferably, the sodium channel blockers exhibit an K_i of 10 μM or less. Most preferably, the sodium channel blockers exhibit an K_i of about 1.0 μM or less. The sodium channel blockers may be tested for their Na^+ channel blocking activity by the following electrophysiological and binding assays.

20

First Electrophysiological Assay:

Cell preparation: HEK-293 cells stably expressing the hSkM1 isoform of Na^+ channels (generous gift from Dr. A. L. George, Vanderbilt University Medical School) were cultured using standard techniques, as described previously (Verdoorn, T.A, *et al.*, *Neuron* 4:919-928 (1990)). For electrophysiology, cells were plated onto 35 mm Petri dishes (pre-coated with poly-D-lysine) at a density of 1:40 on the day of re-seeding from confluent cultures. Cells are suitable for recordings for 2-3 days after plating.

Patch-clamp recordings of voltage-sensitive Na^+ currents: Whole-cell voltage-clamp recordings were made using conventional patch-clamp techniques (Hamill *et al.*, *Pfluegers Arch.* 391:85-100 (1981)) with an

Axopatch 200A amplifier (Axon Instruments, Foster City, CA). Recordings were made within 2-3 hours after neuron dissociation. The recording chamber was continuously superfused with the external solution (150 mM NaCl, 5.4 mM KCl, 1.8 mM CaCl₂, 1 mM MgCl₂, 10 mM HEPES, 10 mM glucose, pH 7.4 (NaOH)) at a speed of about 1 ml/min. Recording pipettes were pulled from thick-walled capillaries (WPI, Sarasota, Fl) and fire-polished. The pipette resistances ranged from 1 to 3 MΩ when the pipettes were filled with internal solution containing (in mM): 110 CsF, 10 NaCl, 5 MgCl₂, 11 EGTA, 10 HEPES, pH adjusted to 7.4 with CsOH. Osmolality was set with a difference of 15-20 mmol/kg between external and internal solutions (lower inside the cell). Drugs and intervening wash-outs were applied through a linear array of flow pipes (Drummond Microcaps, 2-μl, 64-mm length). Compounds are dissolved in dimethylsulfoxide (DMSO) to make a 30 mM stock solution, which was subsequently diluted into the external solution to give final concentrations of 0.1-100 μM. At the highest (1%) concentration, DMSO inhibited the size of Na⁺ current only slightly. Currents were recorded at room temperature (22-25°C), filtered at 5 kHz with an active 8-pole Bessel filter (Frequency Devices, Haverhill, MA), digitized at 10-50-μs intervals, and stored using Digidata 1200 analog/digital interface with Pclamp6/Clampex software (Axon Instruments). Series resistance was cancelled typically by ~75% when necessary. The inhibitory potency of drugs was assessed by measuring reductions in the peak amplitude of Na⁺ currents induced by increasing concentrations of compounds tested. Na⁺ currents were elicited by stepping membrane voltage from holding potentials over the range -100 mV to -50 mV, to a pulse potential of -10 mV. The test pulse duration was 5-10 msec, repeated at a frequency ≤ 1 Hz. Concentration-inhibition curves were fitted with equation 1:

$$I/I_{\text{control}} = 1/(1 + ([\text{compound}]/IC_{50})) \quad \text{Eq. 1}$$

where I_{control} is the maximal Na⁺ current in the absence of antagonist, [compound] is the drug concentration, and IC_{50} is the concentration of compound that produces half maximal inhibition.

Alternate Electrophysiological Assay:

5 *Cell preparation:* HEK-293 (NaIIA-B2) cell line stably expressing the
rBIIA isoform of Na⁺ channels is established in-house. The cells are cultured
using standard techniques, as described previously (Verdoorn, T.A, *et al.*,
Neuron 4:919-928 (1990)). For electrophysiology, cells are plated onto poly-
D-lysine pre-coated Cellware 35 mm Petri dishes (BIOCOAT, Becton
Dickinson) at a density of ~10⁴ cells/dish on the day of re-seeding from
10 confluent cultures. Our experience has been that cells are suitable for
recordings for 2-3 days after plating.

Patch-clamp recordings of voltage-sensitive Na⁺ currents: Whole-cell
voltage-clamp recordings are made using conventional patch-clamp
techniques (Hamill *et al.*, *Pfluegers Arch.* 391:85-100 (1981)) with an
15 Axopatch 200A amplifier (Axon Instruments, Foster City, CA). The recording
chamber is continuously superfused with the external solution (150 mM NaCl,
5.4 mM KCl, 1.8 mM CaCl₂, 1 mM MgCl₂, 10 mM HEPES, 10 mM glucose,
pH 7.4 adjusted with NaOH, osmolality ~320 mmol/kg) at a speed of about 1
mL/min. Recording pipettes were pulled from the thick-walled capillaries
20 (WPI, Sarasota, FL) and fire-polished. The pipette resistances range from 1 to
3 MΩ when the pipettes are filled with internal solution containing (in mM):
130 CsF, 20 NaCl, 2 MgCl₂, 10 EGTA, 10 HEPES, pH adjusted to 7.4 with
CsOH, osmolality ~310 mmol/kg. Drugs and intervening wash-outs are
applied through a linear array of flow pipes (Drummond Microcaps, 2 μL, 64-
25 mm length). Compounds are dissolved in dimethylsulfoxide (DMSO) to
make a 30 mM stock solution, which is subsequently diluted into the external
solution to give final concentrations of 0.1-100 μM. At the highest (1 %)
concentration, DMSO inhibits the size of Na⁺ current only slightly. Currents
are recorded at room temperature (22-25 °C), filtered at 3 kHz with an active
30 8-pole Bessel filter (Frequency Devices, Haverhill, MA), digitized at 10-50 μs
intervals, and stored using Digidata 1200 analog/digital interface with

Pclamp6/Clampex software (Axon Instruments). Series resistance is cancelled typically by ~75% when necessary.

The following voltage pulse protocols are used to assess the potency and kinetics of inhibition of the Na^+ channels by the compounds (Fig. 1).

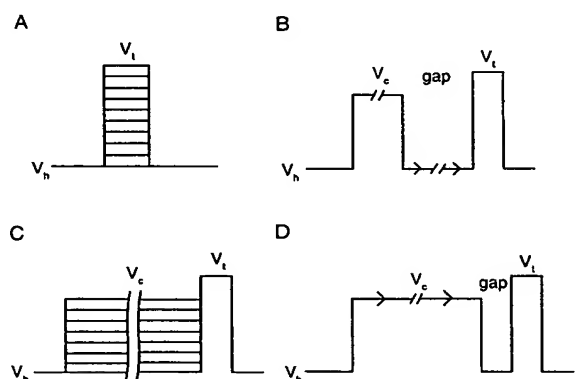


Figure 1. Voltage pulse protocols. A. IV-curves. C. Steady-state inactivation. B. Repriming kinetics. D. Time course of binding.

Current-voltage relationship (IV-curve), protocol A, is used to report the voltage at which the maximal inward Na^+ current is achieved. This voltage is used throughout the experiment as testing voltage, V_t . The steady-state inactivation (or, availability) curve, protocol C, is used to get the voltage at which almost complete ($\geq 95\%$) inactivation of Na^+ channels occurs; it serves as voltage for conditioning prepulse, V_c , throughout the experiment. Protocol B reports how fast the channels recover from inactivation at hyperpolarized voltages. This permits us to set up the duration of the hyperpolarization gap which is used in measurement of the kinetics of binding of compounds to inactivated Na^+ channels (protocol D). Channel repriming under control conditions is fast ($\geq 90\%$ recovery during first 5-10 ms). If a drug substantially retards the repriming process, then it becomes possible (protocol D) to accurately measure the kinetics of binding of the inhibitor to inactivated channels as well as the steady-state affinity (k_+ and K_i). To estimate k_+ values, the reduction in peak currents in successive trials with varying pre-pulse duration is plotted as a function of pre-pulse duration and the time constant (τ) measured by mono-exponential fit. A plot of $1/\tau$ as a function of antagonist

concentration then allows calculating of the macroscopic binding rates of the antagonists. To determine K_i values the partial inhibition curves measured by fractional responses in steady-state are fitted with the logistic equation:

$$I/I_{\text{control}} = 1/(1 + ([\text{antagonist}]/K_i)^p), \quad \text{Eq. 2}$$

5

where I_{control} is the maximal Na^+ current in the absence of antagonist, $[\text{antagonist}]$ is the drug concentration, K_i is the concentration of antagonist that produces half maximal inhibition, and p is the slope factor.

10 ***Binding Assay:***

The ability of sodium channel blockers to modulate either site 1 or site 2 of the Na^+ channel may be determined following the procedures fully described in Yasushi, *J. Biol. Chem.* 261:6149-6152 (1986) and Creveling, *Mol. Pharmacol.* 23:350-358 (1983), respectively. Rat forebrain membranes were used as sources of Na^+ channel proteins. The binding assays are conducted in 130 μM choline chloride at 37°C for 60-minute incubation with [^3H] saxitoxin and [^3H] batrachotoxin as radioligands for site 1 and site 2, respectively.

15

In vivo Pharmacology:

The compounds of the present invention may be tested for *in vivo* anticonvulsant activity after i.v., p.o. or i.p. injection using a number of anticonvulsant tests in mice, including the maximum electroshock seizure test (MES). Maximum electroshock seizures were induced in male NSA mice weighing between 15-20 g and male Sprague-Dawley rats weighing between 200-225 g by application of current (50 mA, 60 pulses/sec, 0.8 msec pulse width, 1 sec duration, D.C., mice; 99 mA, 125 pulses/sec, 0.8 msec pulse width, 2 sec duration, D.C., rats) using a Ugo Basile ECT device (Model 7801). Mice were restrained by gripping the loose skin on their dorsal surface and saline-coated corneal electrodes were held lightly against the two corneae.

25

20

Rats were allowed free movement on the bench top and ear-clip electrodes were used. Current was applied and animals were observed for a period of up to 30 sec for the occurrence of a tonic hindlimb extensor response. A tonic seizure was defined as a hindlimb extension in excess of 90 degrees from the plane of the body. Results were treated in a quantal manner.

The compounds may be tested for their antinociceptive activity in the formalin model as described in Hunskaar, S., O. B. Fasmer, and K. Hole, *J. Neurosci. Methods* 14: 69-76 (1985). Male Swiss Webster NIH mice (20-30 g; Harlan, San Diego, CA) were used in all experiments. Food was withdrawn on the day of experiment. Mice were placed in Plexiglass jars for at least 1 h to accommodate to the environment. Following the accommodation period mice were weighed and given either the compound of interest administered i.p. or p.o., or the appropriate volume of vehicle (10 % Tween-80). Fifteen minutes after the i.p. dosing, and 30 min after the p.o. dosing mice were injected with formalin (20 μ L of 5% formaldehyde solution in saline) into the dorsal surface of the right hind paw. Mice were transferred to the Plexiglass jars and monitored for the amount of time spent licking or biting the injected paw. Periods of licking and biting were recorded in 5 min intervals for 1 hr after the formalin injection. All experiments were done in a blinded manner during the light cycle. The early phase of the formalin response was measured as licking / biting between 0-5 min, and the late phase was measured from 15-50 min. Differences between vehicle and drug treated groups were analyzed by one-way analysis of variance (ANOVA). A P value ≤ 0.05 was considered significant. Having activity in blocking the acute and second phase of formalin-induced paw-licking activity, the compounds are considered to be efficacious for acute and chronic pain.

The compounds may be tested for their potential for the treatment of chronic pain (antiallodynic and antihyperalgesic activities) in the Chung model of peripheral neuropathy. Male Sprague-Dawley rats weighing between 200-225 g were anesthetized with halothane (1-3 % in a mixture of 70 % air and 30 % oxygen) and their body temperature controlled during anesthesia through use of a homeothermic blanket. A 2-cm dorsal midline incision was

then made at the L5 and L6 level and the para-vertebral muscle groups retracted bilaterally. L5 and L6 spinal nerves were then be exposed, isolated, and tightly ligated with 6-0 silk suture. A sham operation was performed exposing the contralateral L5 and L6 spinal nerves as a negative control.

5 *Tactile Allodynia:* Rats were transferred to an elevated testing cage with a wire mesh floor and allowed to acclimate for five to ten minutes. A series of Semmes-Weinstein monofilaments were applied to the plantar surface of the hindpaw to determine the animal's withdrawal threshold. The first filament used possessed a buckling weight of 9.1 gms (.96 log value) and was applied
10 up to five times to see if it elicited a withdrawal response. If the animal had a withdrawal response then the next lightest filament in the series would be applied up to five times to determine if it could elicit a response. This procedure was repeated with subsequent lesser filaments until there was no response and the lightest filament that elicited a response was recorded. If the
15 animal did not have a withdrawal response from the initial 9.1 gm filament then subsequent filaments of increased weight were applied until a filament elicited a response and this filament was then recorded. For each animal, three measurements were made at every time point to produce an average withdrawal threshold determination. Tests were performed prior to and at 1, 2,
20 and 24 hrs post drug administration. Tactile allodynia and mechanical hyperalgesia tests were conducted concurrently.

Mechanical Hyperalgesia: Rats were transferred to an elevated testing cage with a wire mesh floor and allowed to acclimate for five to ten minutes. A slightly blunted needle was touched to the plantar surface of the hindpaw
25 causing a dimpling of the skin without penetrating the skin. Administration of the needle to control paws typically produced a quick flinching reaction, too short to be timed with a stopwatch and arbitrarily given a withdrawal time of 0.5 sec. The operated side paw of neuropathic animals exhibited an exaggerated withdrawal response to the blunted needle. A maximum
30 withdrawal time of ten seconds was used as a cutoff time. Withdrawal times for both paws of the animals were measured three times at each time point with a five-minute recovery period between applications. The three measures

were used to generate an average withdrawal time for each time point. Tactile allodynia and mechanical hyperalgesia tests were conducted concurrently.

The compounds may be tested for their neuroprotective activity after focal and global ischemia produced in rats or gerbils according to the procedures described in Buchan *et al.* (*Stroke*, Suppl. 148-152 (1993)) and Sheardown *et al.* (*Eur. J. Pharmacol.* 236:347-353 (1993)) and Graham *et al.* (*J. Pharmacol. Exp. Therap.* 276:1-4 (1996)).

The compounds may be tested for their neuroprotective activity after traumatic spinal cord injury according to the procedures described in Wrathall *et al.* (*Exp. Neurology* 137:119-126 (1996)) and Iwasaki *et al.* (*J. Neuro Sci.* 134:21-25 (1995)).

The invention also relates to a kit for the treatment of chronic pain or convulsions comprising a carrier containing one or more containers one of which comprises a sodium channel blocker and another of which comprises at least one of gabapentin and pregabalin. Examples of such carriers include boxes, tubes and the like that are used to package pharmaceuticals. Examples of containers include bottles, jars, tubes and the like.

The following examples are illustrative, but not limiting, of the method and compositions of the present invention. Other suitable modifications and adaptations of the variety of conditions and parameters normally encountered in clinical therapy and which are obvious to those skilled in the art are within the spirit and scope of the invention.

Example 1

Coadministration of Co 102862 and Gabapentin

The tactile antiallodynia effect of Co 102862 and gabapentin was tested alone or in combination in the Chung model of neuropathic rats. As shown in FIG. 1, rats that received 1.25 mg/kg Co 102862 p.o. showed moderate antiallodynia effect whereas 25 mg/kg gabapentin s.c. exhibited minimum or no effect when given alone. However, when both compounds were given together, a much greater withdrawal threshold was observed than if

one were to add the effect of Co 102862 and gabapentin given individually. Thus, the combination of the two drugs has a synergistic effect. See FIG. 1.

5 Having now fully described this invention, it will be understood by those of ordinary skill in the art that the same can be performed within a wide and equivalent range of conditions, formulations and other parameters without affecting the scope of the invention or any embodiment thereof. All patents, patent applications and publications cited herein are fully incorporated by reference herein in their entirety.